REMARKS/ARGUMENTS

With this amendment, claims 1 and 5-9 are pending. For convenience, the Examiner's rejections are addressed in the order presented in the October 29, 2003, Office Action. Applicants thank Examiner Ford and her supervisor Examiner Smith for there time in allowing an interview with Applicant's representative Beth Kelly and Joe Snyder on February 3, 2004. The arguments to overcome the rejection under 35 U.S.C. §103(a) were discussed, but no agreement was reached.

I. Status of the claims

Claim 1 is amended to recite that the IgG4 immunoglobulin has a decreased risk of aggregating and fragmenting when manufactured using the claimed methods. Support for this amendment is found throughout the specification, for example at page 2, lines 16-21. This amendment is not a limiting amendment and adds no new matter.

II. Rejections under 35 U.S.C. §103(a)

A. Introduction

Claims 1 and 5-9 are rejected under 35 U.S.C. 103(a) as allegedly obvious over Laursen *et al.* (U.S. Patent No. 6,281,336) in view of Flaa *et al.* (U.S. Patent 6,165,336). In response, Applicants respectfully traverse the rejection.

Laursen *et al.* disclose methods of purifying a total IgG preparation from plasma. Laursen *et al.* disclose that the purpose of the IgG preparation is in treating patients with disease or conditions that benefit from replacement or supplementation of the total IgG component of blood, including *e.g.*, primary and secondary agammaglobulinemia, Wiskott-Aldrich syndrome, sever combined immunodeficiency, treatment of autoimmune diseases, treatment of certain patients with immune conditions. See, *e.g.*, Laursen *et al.* at column 15, lines 8-47. Laursen *et al.* first adjust the pH of plasma to a pH lower than 6.0, *e.g.*, preferable pH 5.4. See, *e.g.*, Laursen *et al.*, at column 5, lines 12-17. After additional steps, including elution from anion and cation exchange resins, Laursen *et al.* arrive at their disclosed product, a total IgG preparation

which requires subtype distribution close to that of blood. See, *e.g.*, Laursen *et al.*, column 20, lines 9-15. Laursen *et al.* disclose the IgG subclass distribution in their total IgG product and in commercially available total IgG products in percentage form in a Table at columns 17 and 18. The percent IgG4 in these products ranges from 0.6% to 1.5% and is described as being within the subclass distribution range of blood. Flaa *et al.* teach solutions for stabilizing proteins, which, in some embodiments, include sugars such as lactose, as bulking agents.

In contrast, the claimed invention is a method of manufacturing purified *IgG4 immunoglobulin subtype*, free of IgG1, IgG2 and IgG3 subtypes for the treatment of allergic reactions, including serious insect sting allergies. As a first step, the pH of plasma is adjusted to a value of about 6.5. The plasma is then subjected to anion exchange chromatography, followed by cation exchange chromatography to obtain an IgG4 preparation that is essentially free of other IgG subtypes.

In order to establish a *prima facie* case of obviousness the Office Action must demonstrate that the cited references provide a suggestion or motivation for their modification or combination, a reasonable expectation of success in the combination, and that the references teach or suggest all the claim limitations. All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

Particular care must be taken to avoid use of hindsight in obviousness analysis. According to 35 U.S.C. §103(a), a claimed invention is unpatentable if the differences between it and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." The phrase "at the time the invention was made" ensures that obviousness analysis is performed without the benefit of impermissible hindsight. The Federal Circuit has ruled that

> . . . the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine

> prior art references. . . . Combining prior art references without evidence of such a suggestion, teaching, or motivation simply takes the inventor's disclosure as a blueprint for piecing together the prior art to defeat patentability--the essence of hindsight. *In re Dembiczak*, 50 USPQ2d 1614, 1617 (1999), citations omitted.

The Federal Circuit recognizes that evidence of a suggestion, teaching or motivation to combine can be found in a number of sources. However, actual evidence of a suggestion, or teaching, or motivation to combine is required and the showing of a suggestion, or teaching, or motivation to combine must be "clear and particular." *Id.*

As discussed below the cited references fail to support a prima facie case of obviousness. None of the cited references provide the required clear and particular evidence of a suggestion, teaching, or motivation for their combination. In addition, the cited references, alone or in combination, fail to provide all the elements of the claimed invention.

B. *The cited art does not teach or suggest all the elements of the claimed invention.*

Laursen *et al.* teaches use of different method steps then the steps recited in the claims. Laursen *et al.* also arrive a different end product then the purified IgG4 recited in the claims. Flaa *et al* is silent as to stabilization of immunoglobulin proteins.

1. The cited art uses different method steps.

The cited art teaches, as a first step, adjusting the pH of a plasma protein containing fraction to a pH below 6, preferably 5.4. (See *e.g.*, Lausen *et al.* at column 5, lines 9-17.) In contrast, the claims recite as a first step adjusting the pH of plasma to about 6.5. Clearly, a pH of 6.5 is greater than the maximum pH 6 recited by Laursen *et al.*, and thus the method of Laursen is not encompassed by the claims.

Laursen *et al.* also teach away from use of pH values greater than six, as used in the claimed methods. Laursen *et al.* state that a pH below 6.0 is required to solubilize the total IgG proteins in a subsequent PEG precipitation step. Therefore, Laursen *et al.* teach away from

use of pH values greater than 6, *e.g.* the claimed 6.5 pH value. Lacking the claimed adjustment of plasma pH to a value of 6.5, Laursen *et al.* fail to teach all the steps of the claimed method.

2. The cited art teaches manufacture of a different product.

Laursen *et al.* teach manufacture of an IgG preparation with 1.5% IgG4 subtype, *i.e.*, 98.5% of the IgG molecules are subtypes IgG1, IgG2, or IgG3. The present claims recite as a final product, a cationic effluent comprising IgG4 that is essentially free of other IgG subtypes. In the telephone interview, Examiners Ford and Smith speculated that other IgG subtypes are present in the final products in amounts similar to those disclosed in Laursen *et al.* Applicants assert, first, that the meaning of essentially free of other IgG subtypes is clear on its face to those of skill and refers to a product that has very high levels of IgG4 relative to other IgG subtypes, *e.g.*, at least 95% IgG4. Second, the specification provides a measure of the amount of IgG4 subtype in the final product at page 7, lines 26-27. "[The cation] effluent is mostly, if not entirely, IgG4." Third, evidence of the composition of the final IgG4 product has been provided to the Examiner in a declaration from inventor William Pollack, submitted January 31, 2002. (Resubmitted as Exhibit A.) At page 3, paragraph 7, Dr. Pollack states that the product of the claimed method is "an IgG4 preparation free of other subtypes." While the claims are not rejected under 35 U.S.C. §112, second paragraph, Applicants respectfully assert that the meaning of " IgG4 essentially free of other IgG subtypes" is clear to those of skill and does not encompass the product disclosed in Laursen *et al.* Thus, the product of the claimed methods is not disclosed in Laursen *et al.*, or in any other reference cited in the Office Action.

The Office Action also appears to assert that a table in Laursen *et al.* at columns 17 and 18 discloses a purified IgG4 preparation. This interpretation is incorrect. Laursen *et al.* characterize the IgG subclass distribution in their total IgG product and in commercially available total IgG products in percentage form in the table at columns 17 and 18. The percent IgG4 in these products ranges from 0.6% to 1.5% and is described as being within the subclass distribution range of blood. Applicants respectfully assert that the disclosure that 1.5% of the IgG in the Laursen *et al.* product is IgG4 does not mean that IgG4 has been purified away from

other IgG molecules. IgG subclass distribution reported in the table was determined using immunodiffusion assays (see, *e.g.*, Laursen *et al.* at column 20, lines 6-8) which rely on binding of additional immunoglobulins to the IgG4 molecules for detection. Thus, even if the characterization of the amount of IgG4 by immunodiffusion could somehow be construed to be a purification step, the IgG4 detected in the immunodiffusion assay is not essentially free of other IgG subtypes as maintained by the Office Action.

Because neither the product of Laursen *et al.*, nor the product of the immunodiffusion assay are IgG4 that is essentially free of other IgG subtypes, Laursen *et al.* does not teach or disclose the products of the claimed methods.

C. *The cited art does not provide one of skill with a suggestion for modification or combination to arrive at the claimed invention.*

Laursen *et al.* provide no clear and particular suggestion or motivation for its combination with Flaa *et al.* to arrive at the claimed invention. First, Laursen *et al.* do not provide any suggestion or teaching of use of a purified IgG4 subtype, or any purified IgG subtype as a therapeutic. Laursen *et al.* teach only the therapeutic use of a total IgG4 composition with subtype distribution close to that of human blood, *i.e.*, 1-3% IgG4. Second, Laursen *et al.* teach only treatment of disease or conditions that benefit from replacement or supplementation of the total IgG component of blood, and for that purpose Laursen *et al.* explicitly require a total IgG preparation with subtype distribution close to that of human blood, *i.e.*, 1-3% IgG4, for that use. See, *e.g.*, Laursen *et al.* at column 20, lines 9-15. Flaa *et al.* teach only solutions for stabilizing purified proteins and do not teach any methods for purifying proteins, including immunoglobulins. Thus, neither Laursen *et al.* nor Flaa *et al.* provide the clear and particular suggestion or motivation for their combination to arrive at the claimed invention.

In addition, Applicants respectfully remind the Examiner that there cannot be an adequate suggestion or motivation to make a proposed modification where such modification renders the prior art unsuitable for its intended purpose. *In re Gordon*, 221 USPQ 1125 (Fed.

Cir. 1984); MPEP §2143.02. Modification of Laursen *et al.* to arrive at a purified IgG4 subtype to be "combined" with Flaa *et al.* would render the product unsuited to the use intended by Laursen *et al.* Laursen *et al.* discloses a method of purifying a total IgG preparation from other plasma proteins with the intention of using the IgG preparation to treat patients with diseases or conditions that benefit from replacement or supplementation of the total IgG component of blood. Even if the teachings of Laursen *et al.* could be modified to arrive at a purified IgG4 preparation, as suggested by the Office Action (Laursen *et al.* specifically disclaim adjustment of plasma to pH values greater than 6.0), a purified IgG4 preparation would not be useful to treat diseases or conditions that benefit from replacement or supplementation of the total IgG component of blood. Thus, the combination of Laursen *et al.* with Flaa *et al.* found in the Office Action cannot be used as intended by the references, and cannot be assumed to provide a motivation or suggestion for their combination.

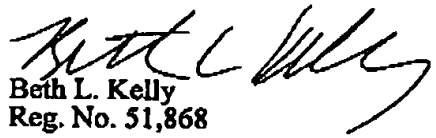
In view of the above amendments and remarks, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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